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EXAMINER

PRATS, FRANCISCO CHANDLER

ART UNIT PAPER NUMBER

1651

DATE MAILED: 09/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/888,734

Applicant(s)

ROSER, BRUCE JOSEPH

Examiner

Francisco C Prats

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-16 and 20-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14-16 and 20-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

The amendment filed June 14, 2004, has been received and entered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claims 14-16 and 20-22 are pending and are examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis et al (U.S. Pat 5,824,780) in view of Livesey et al (U.S. Pat. 5,364,756).

The '780 patent describes a process of producing an activated and stabilized Factor VIII in the absence of albumin. See claim 1, at column 9. The Factor VIII is clearly separated from albumin, as evidenced by the removal of "other proteins" from the Factor VIII preparation. See step (b) of claim 1, at

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column 9, line 46 through column 10, line 3. The Factor VIII is stabilized by the addition of a stabilizing additive which may be trehalose. See claim 4, at column 10. Note the recitation of trehalose and albumin as *alternative* stabilizing additives. The '780 patent also describes that after preparation of the stabilized solution of Factor VIII, the Factor VIII is lyophilized. See claim 5, at column 10.

See also, the discussion at col. 5, lines 30-43, stating that "[e]xamples of stabilizers include albumin ... and trehalose", and that "[f]ollowing preparation and stabilization of the activated Factor VIII, the protein can be lyophilized and stored at reduced temperatures" Col. 5, lines 4-6. Note that the '780 patent lists recombinant Factor VIII as being suitable for use in the disclosed process. Column 2, lines 61, et seq. Thus, taken as a whole, the '780 patent clearly describes a process wherein an aqueous solution of Factor VIII in the absence of albumin is lyophilized in the presence of trehalose, are cited in the claims.

The '780 patent differs from the claims under examination by failing to describe the lyophilization of native Factor VIII, as recited in claim 15. However, Livesey clearly provides motivation for lyophilizing "native" Factor VIII in trehalose without albumin by not only claiming a specific embodiment

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(claim 17) of lyophilizing Factor VIII, but also disclosing that trehalose, and not albumin, is one of a number of agents particularly suited to dry preservation of macromolecules such as proteins. See col. 9, lines 16 -32:

For example, trehalose and polyhydroxyl carbohydrates bind to and stabilize macromolecules such as proteins and nucleic acids in a virus or vaccine sample when dried, thereby protecting the integrity of the sample. Various dry protectants can be used in the present invention: sucrose, raffinose, trehalose, zinc, proline (or other protein stabilizers), myristic acid (a known thermostabilizer of vaccines), spermine (a polyanionic compound) and combinations thereof.

Thus, the artisan of ordinary skill seeking to preserve the "native" Factor VIII encompassed by Livesey's claim 17, recognizing that Factor VIII is a protein, clearly would have looked to trehalose instead of albumin, based on Livesey's disclosure that trehalose is one of a number of agents particularly suited for protein protection in freeze-drying procedures, and albumin is not. Additional motivation for freeze-drying Factor VIII using trehalose in the absence of albumin would have been derived from the fact that the lone example of protein freeze-drying of Livesey, Example 5 at columns 23 and 24, demonstrates that the integrity of a protein-containing viral vaccine is adequately protected by trehalose in buffer with no other preservative agents.

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Claims 14-16 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis et al (U.S. Pat 5,824,780) in view of Livesey et al (U.S. Pat. 5,364,756) as applied to claims 14-16 above, and further in view of Bhattacharva et al (U.S. Pat. 5,288,853).

As discussed above, the '780 patent and Livesey clearly provide motivation for lyophilizing an aqueous solution of albumin-free Factor VIII, recombinant or native, in the presence of trehalose. While neither reference directly describes the use of histidine in the lyophilization milieu for Factor VIII, Bhattacharva clearly discloses that histidine is a preferred buffer for use in Factor VIII preparations to be lyophilized. See column 7, lines 19-22. ("Histidine is preferred as a buffer in the purification, since the final lyophilized Factor VIII is more easily resolubilized when it is in a buffer comprising histidine.") Thus, the artisan of ordinary skill, recognizing the advantages of including histidine in the lyophilization milieu for Factor VIII, clearly would have been motivated to have included histidine the aqueous solutions used in the processes of Curtis and/or Livesey. A holding of obviousness is therefore required.

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Response to Arguments

All of applicant's argument has been fully considered but is not persuasive of error. Applicant urges initially that because the active and native forms of Factor VIII are very different, one looking to preserve native Factor VIII would not look to the Curtis (the '780 patent) disclosure of preserving active Factor VIII for methods of preserving native Factor VIII. However, it is truly unfair to characterize the activated and native forms of Factor VIII as being "very different."

In fact, the proteins possess numerous virtually identical amino acid sequences. While the activating cleavage event does change the three dimensional structure of the molecule, such that the activated form acts as a protease, at the very least Curtis establishes generally that Factor VIII has a therapeutic utility which can be preserved upon freeze-drying in the presence of trehalose. Moreover, it is respectfully pointed out that Curtis is relied upon in combination with other references. Thus, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231

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USPQ 375 (Fed. Cir. 1986). In sum, one looking for suitable methods of preserving native Factor VIII would clearly consider Curtis' methods of preserving activated Factor VIII relevant, since the two proteins are very similar in very many aspects, and would therefore be expected to be preserved by similar preservative agents.

Applicant further argues that because Livesey describes preserving "suspensions" of biological material, and not aqueous "solutions" as recited in the claims under examination, and because the cited Example 5 does not describe preservation of compositions containing solely protein, one of ordinary skill seeking to preserve native Factor VIII would not follow the teachings of Livesey when preserving solutions of Factor VIII.

However, the non-chemical, non-scientific dictionary relied upon by applicant to differentiate between the terms "suspension" and "solution" does not provide proper scientific definitions for the terms in question. More importantly, the non-chemical, non-scientific dictionary relied upon by applicant does not serve to distinguish the claims from the prior art.

At bottom, whether one terms the intermediate aqueous product a "solution" or a "suspension," both Curtis and Livesey suggest preserving Factor VIII by doing exactly what applicant's claims recite -- placing Factor VIII in water which contains

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trehalose, and freeze-drying (i.e. lyophilizing) the product. While applicant urges that Livesey is not relevant to the claims because of the "suspension" terminology used therein, applicant's argument ignores the fact that the "suspension" of Livesey is no different than the "aqueous solution" recited in applicant's claims. Moreover, applicant's argument is entirely undermined by the fact that one of the specifically claimed embodiments in Livesey is the lyophilization of Factor VIII. See claim 17, at column 26. Contrary to applicant's argument, there is nothing in this claimed embodiment suggesting the presence of any biological product other than Factor VIII, and there is nothing in claim 17 of Livesey which requires albumin.

In sum, Livesey clearly suggests doing exactly as claimed - placing Factor VIII in water, along with trehalose, and lyophilizing the resulting product. Combined with Curtis' disclosure, one of ordinary skill clearly would have had a reasonable expectation that Livesey's albumin-free preservative techniques would have functioned with native Factor VIII. Again, at bottom, as evidenced by the cited prior art, applicant's claims are directed to freeze-drying a therapeutic protein known to be desirably freeze-dried, in the presence of a notoriously well-known cryoprotectant, trehalose. The holding of obviousness must therefore be maintained.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

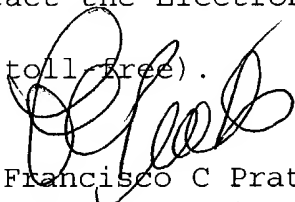
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can

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be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Francisco C Prats
Primary Examiner
Art Unit 1651

FCP